THE RELATION OF THE BONE MARROW TO THE LYMPHATIC SYSTEM

ITS RÔLE IN THE SPREADING OF CARCINOMATOUS METASTASES THROUGHOUT THE SKELETON *

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The study of the lymphatic system still remains far from completed. The question of the relation of the lymphatics to the two most important systems of the animal body, the central nervous system and the bone marrow system, has been especially obscure. There has existed a widespread opinion that the brain is entirely lacking in independent (not perivascular) lymph channels. Unbelievable as it is, that the lymph circulation in the most delicate tissue in the body—the brain substance—is dependent for its metabolism on the perivascular lymphatics, this opinion was supported by such authorities as His [1] and Retzius. Bevan Lewis [2] was the first to raise the question of an intervascular lymphatic system, independent of the perivascular and intravascular systems; once raised, this question never disappeared from the literature until Meynert proved clinically and Kronthal [3] morphologically that there are lymphatics of the cortex of the brain independent of the blood system.

The study of the circulation of lymph in the bone marrow possesses a similar history. Even the question of the blood channels in the bone marrow is still a much disputed one, in spite of the thorough and recent work of Drinker and Lund,[4] and of Doan.[5] It seems, however, to be the opinion of the majority that the blood capillaries of bone marrow are a closed canal system lined with endothelium.

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1. His, W.: Ueber ein perivasculäres Kanalsystem in den nervösen Centralorganen und ueber dessen Beziehungen zum Lymphsystem, Ztschr. f. wissensch. Zool. **15**:127, 1865.

2. Bevan, Lewis: A Textbook of Mental Diseases With Special Reference to the Pathological Aspects of Insanity, London, 1889, p. 80.

3. Kronthal, Paul: Lymphcapillaren im Gehirn, Neurol. Centralbl. **9**:679, 1890.

4. Drinker, C. K.; Drinker, K. R., and Lund, C. C.: Circulation in the Mammalian Bone Marrow, Am. J. Physiol. **62**:1 (Sept.) 1922.

5. Doan, C. A.: The Capillaries of the Bone Marrow of the Adult Pigeon, Bull. Johns Hopkins Hosp. **33**:222 (June) 1922.

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Tillmanns and Budge were the first to take up the matter of the lymph circulation in the skeleton. Tillmanns [6] confined his work to the circulation of lymph in the joints. In his paper on this subject, he came to the conclusion that the hyaline cartilage covering the articular surfaces of the bones has no lymph vessels. Budge [7] mentions perivascular lymphatics in the substantia compacta of the bones. In recent literature, the work of Rauber [8] is the most outstanding; he asserts that the haversian canals are lined with endothelium. This endothelium forms the external wall of the perivascular lymph channels surrounding the singular or multiple blood capillaries, coursing in the central portion of the haversian canals. These perivascular lymphatics anastomose widely with the abundant lymphatics of the periosteum. Prussian blue injected into the periosteal lymphatics freely penetrates the substantia compacta and stops abruptly at the endosteum (perimedullary space). In the last edition of Morris' anatomy, Clark [9] writes concerning the lymph circulation in the bones as follows: "Lymph capillaries have also been described accompanying the blood vessels in the haversian canals in bones. Nothing is known concerning the lymphatics of the bone marrow." A more definite statement was made by Roger and Josué; they denied the existence of lymphatics in the bone marrow; in a special monograph [10] dealing with the histology of the bone marrow, these authors state: "Il n'existe pas de vaisseaux lymphatiques dans la moelle des os." The only experimental study of this question was made by Piney [11] in 1922. This author attempted to demonstrate the lymphatics of the bone marrow by direct injection with Prussian blue. His failure to obtain any results led him to the conclusion that the bone marrow is lacking in lymph channels. This is the stage in which the subject has remained until the present day.

It was unbelievable to us that a complexity of tissue rich in connective tissue elements and supplied with abundant blood vessels would be lacking in lymph vessels. Such a fact would not be in accord with the present day views concerning tissues derived from the mesoderm. However, before taking up again this matter, after all the categorical denials

6. Tillmanns, H.: Die Lymphgefässe der Gelenke, Arch. f. microscop. Anat. **12**:649, 1876.

7. Budge, A.: Die Lymphwurzeln der Knochen, Arch. f. mikr. Anat. **13**:87, 1877.

8. Rauber, A.: Rauber's Lehrbuch der Anatomie des Menschen, Leipzig, 1911, pp. 5 and 17.

9. Clark, Eliot R.: Morris' Human Anatomy, Ed. 7, Philadelphia, P. Blakiston's Son & Co., 1923, p. 735.

10. Roger and Josué: La Moelle osseuse a l'état normal et dans les infections, Paris, 1899, p. 5.

11. Piney, A.: The Anatomy of the Bone Marrow, Brit M. J. **2**:792 (Oct.) 1922.

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of the existence of lymph channels in the bone marrow, it was necessary to account for possible errors in the technic of Piney's investigation. The highly delicate structure of the bone marrow, with its multitude of thinly walled capillaries and loosely interwoven parenchyma, seemed to argue against any methods of study based on injection, i. e., the forcing of foreign material into the medullary cavity. The most favored methods of studying lymph vessels by injection since Sappey and Gérota, I believe, are absolutely not applicable in the study of the lymph

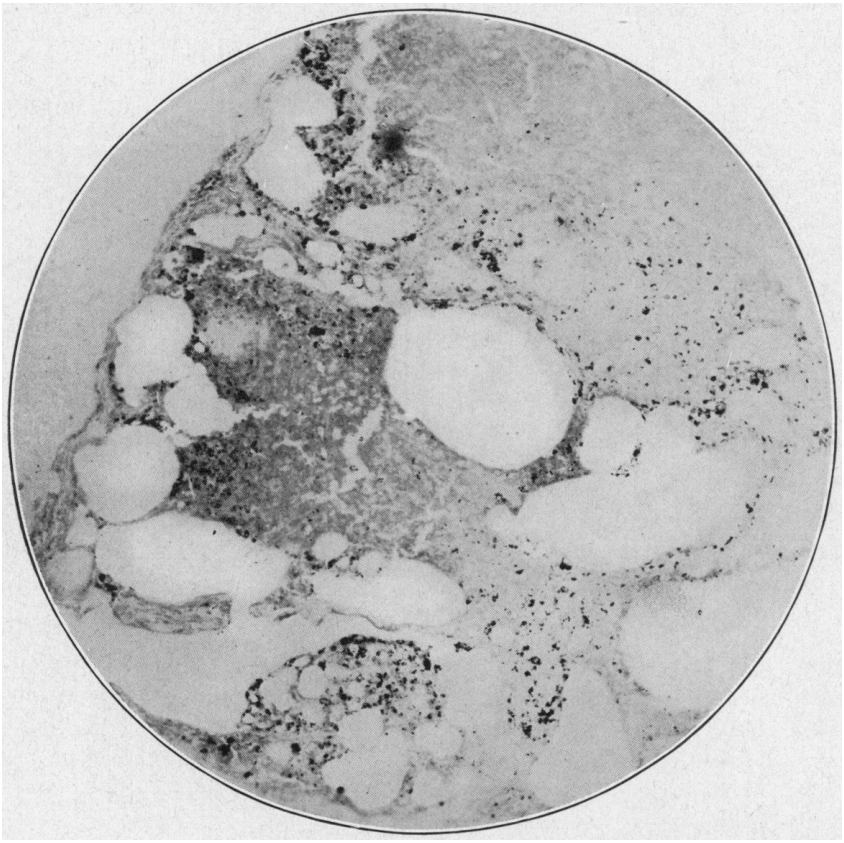

Fig. 1.—Iliac lymph node of a dog (magnification, 80 diameters), two weeks after the introduction of India ink into the medullary cavity of the femur. Carbon particles are transported to and deposited in the lymph node.

vessels of the bone marrow. When Piney was trying to force his injecting mass into the lymph channels of the bone marrow, he always noticed an injection of the blood capillaries. It was obvious to me that unless I refrained from this method of study I would be doomed to failure. I chose a physiologic way of study, based on the same principle as the known doctrine spoken of as Cohnheim's law. This doctrine states that the tubercle bacillus reveals the seat of its entry into the body by producing specific changes in the lymph nodes that receive

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lymphatics from the area in which it enters. It is known that, if a soluble material is injected hypodermically, it passes into the connective tissue spaces, and is taken up by the blood capillaries; in the interchange of soluble material in the tissues, the physical conditions are all in favor of its direct entry into the blood. If the injected material is insoluble, its destination is different; the solid particles are taken up by phagocytic cells, some of which enter the lymphatics. These are carried to the lymph nodes. Considering these facts, our hypothesis was: If the bone marrow has any relation to the lymph system, foreign material, introduced into the medullary cavity, will be transported to and appear in lymph nodes, which will be regional lymph nodes of the bone marrow of the respective bone. My idea was to introduce a few drops of India ink or carmin emulsion into the medullary cavity of a bone, and, at a later date, to examine the main groups of the lymph nodes in the adjoining regions of the body.

My experiments were conducted on the femur, tibia, fibula, humerus, radius and ulna of dogs. Through a small incision the diaphysis of the bone was exposed, the periosteum stripped and a hole 2 mm. in diameter drilled through the substantia compacta into the medullary cavity. After the removal of the drill, blood began to flow from the medullary cavity. I waited until the bleeding stopped of its own accord, showing that the pressure in the medullary cavity was not above that on the outside (atmospheric). By means of a specially made needle, from three to five drops of India ink or carmin were introduced into the medullary cavity. After the removal of the needle, the hole in the bone was carefully examined to see if any fluid had escaped from the medullary cavity, which would indicate that the fluid introduced was under a pressure higher than atmospheric. Every case in which this sign of increased pressure in the medullary cavity was observed was discarded and no further study was made of it. In the other cases, the hole in the bone was closed with Horsley's wax and the wound sutured.

The animals were killed in from one to three weeks after the operation. An examination of the lymph nodes of the adjoining regions of the body revealed the following: As early as from twelve to fourteen days after the operation we could recognize, grossly, carbon particles or carmin deposited in certain groups of lymph nodes. A microscopic study revealed this foreign material present in the lymph nodes at an even earlier date, from five to seven days after the operation. Carbon particles reached the periphery of the gland in the interior of phagocytic cells, and passed into the subcapsular sinuses, where they lay in the meshes of the fine network of reticulated fibers and endothelial cells. These pigment carrying cells did not pass completely through the gland, but found their way from the sinuses into the lymphoid nodules of the

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cortex and the lymphoid cords of the medulla. At a later date, they penetrated the middle of the germ centers. In every case of operation on any of the long bones of the lower extremity, the same group of lymph nodes showed a deposit of foreign material; similarly, another definite group of lymph nodes showed a deposition of the foreign granules in every case of the bones of the upper extremity. In the cases of the bones of the lower extremity, these lymph nodes are, in a dog, the iliac nodes. I divide these nodes into two groups; the external

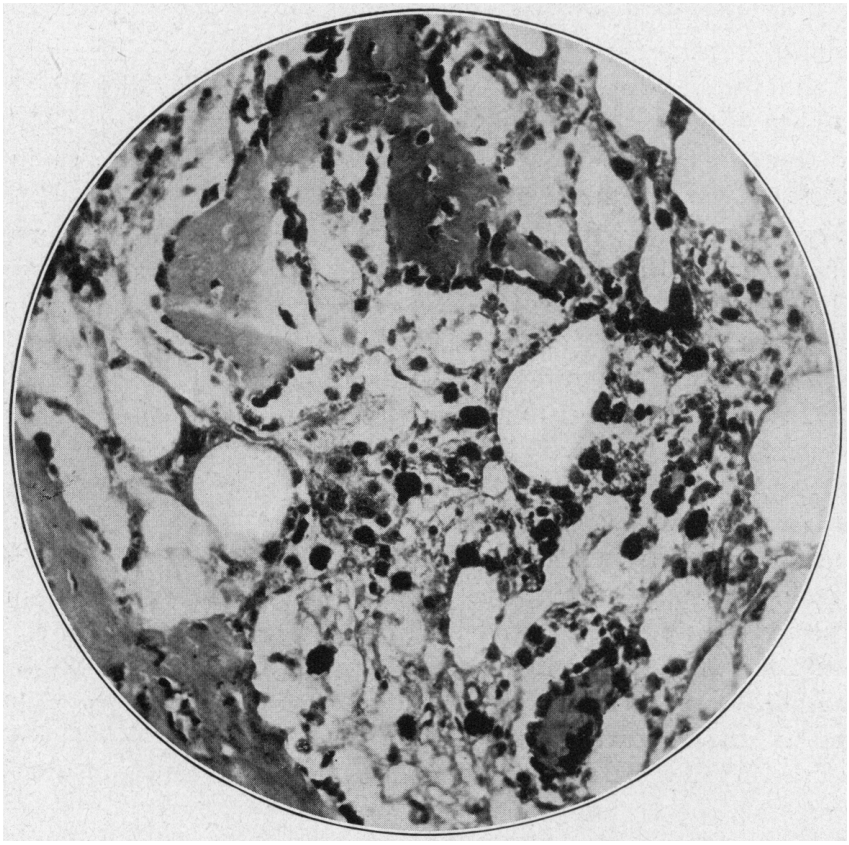

Fig. 2.—Bone marrow of a dog (magnification, 230 diameters) three weeks after the introduction of India ink into the medullary cavity of the femur. The carbon particles, which had not left the medullary cavity, are taken up by various reticular elements of the bone marrow.

group corresponding to the external chain of the external iliac group in man, and the internal group corresponding to the hypogastric lymph nodes in man. In cases of the long bones of the upper extremity, the involved lymph nodes were the cervical lymph nodes, between the cucullaris superior, levator scapulae ventralis and sternocleidomastoides muscles. In man, they correspond to the supraclavicular lymph nodes (lymphoglandulae cervicales profundae inferiores). A most careful

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examination of the identical lymph nodes of the opposite side as well as of the other lymph nodes of the body revealed no trace of the foreign material introduced into the medullary cavity.

These results led us to conclude that the bone marrow has a definite lymph circulation, and that the groups of lymph nodes described are the regional lymph nodes of the long bones of the lower and upper extremities, respectively. In other words, these lymph nodes drain the lymph circulating in the bone marrow. In analogy with the regional lymph nodes of other regions, we expected these lymph nodes to respond also to inflammatory conditions of the bone marrow of the respective bone. To cover this point, another series of experiments was conducted. The technic used in these experiments was the same as that described above, except that a drop of an emulsion of streptococci or staphylococci was introduced into the bone marrow. Thirty-six hours were sufficient in two cases to produce a very marked reaction in the regional lymph nodes of the experimented bones, while the bone marrow showed an extensive abscess. In all other cases of this series, an energetic response of the regional lymph nodes was obtained.

A study of the distribution of the particles of foreign material still remaining in the bone marrow showed that these particles had been taken up by various large cells of the endothelial type. Whether or not some of these impregnated cells were enclosed in lumina of certain tubular structures, which we would expect to be lymph channels of the bone marrow, I do not know positively.

At this stage in the experimental study, it was apparent that the results, although they proved beyond any doubt that there was a definite direct relationship between the bone marrow and the lymphatic system, were not sufficiently obvious from the standpoint of the dogmatic morphologist to prove that the bone marrow is supplied with lymph vessels, since these results were obtained from clinical and pathologic data and not from direct observation of these lymph channels. By means of further study an attempt was made to clear up this point. A careful examination of the soft tissues surrounding the femur of dogs that had been operated on led to the discovery of a vessel impregnated with the same material introduced into the medullary cavity at the time of the operation. This channel, never described before, was found to be a permanent, anatomic structure in the femur of the dog. It pierces the bone obliquely, appearing on the surface, on the anterior aspect, immediately beneath the linea intertrochanterica. In some cases, it was possible to trace this channel for a distance of 2 inches (5.08 cm.). Histologically, this channel consists of an endothelial lining covered with a diffuse, connective tissue sheath, in which the elastic and muscular elements are irregularly scattered. The impregnation of this vessel

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with the foreign material introduced into the medullary cavity leads me to the conclusion that this is the lymphatic trunk draining the lymph of the bone marrow of the femur.

COMMENT

In a consideration of probable errors in the conclusions obtained from the results of the previously described experiments, it is necessary to consider just one probability; this possibility is that the foreign material introduced into the medullary cavity passed through the peri-

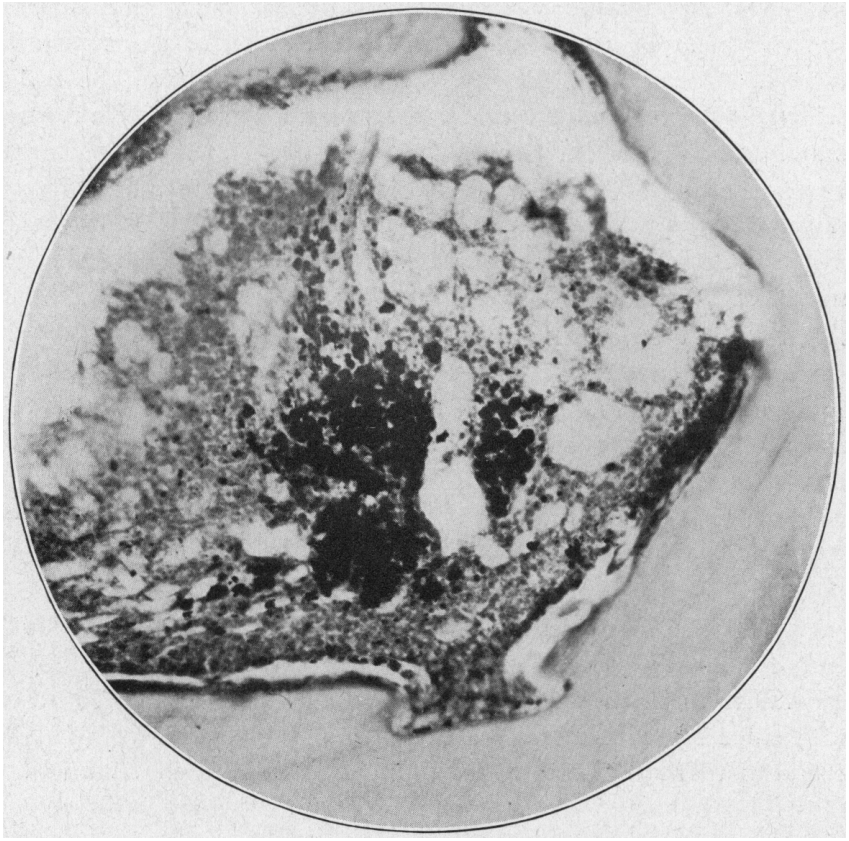

Fig. 3.—Section of the "lymph channel" (magnification, 150 diameters), through which foreign material introduced into the medullary cavity of the femur leaves the bone. The section was taken at the point where the channel pierces the bone from within the medullary cavity.

vascular lymphatics of the substantia compacta into the periosteal lymph vessels. and from there was transported to the lymph nodes. In this case, it would be necessary to consider the lymph nodes described above as regional lymph nodes of the periosteum and substantia compacta of the respective bone, and not of its medullary cavity and bone marrow. My conclusions are free from such an error; this was learned from the fact that, in every case, the periosteum and soft tissues covering the

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drilled bone did not show the slightest trace of the foreign material introduced into the medullary cavity, and in no case did the substantia compacta of the bone show a trace of foreign material in the haversian canals.

The whole question of the existence of a perivascular lymphatic system in the substantia compacta, as described by Rauber, is somewhat problematic. An experiment conducted for the purpose of covering the point of possible transmission of foreign material from the medullary cavity through the substantia compacta led me to take this point of view. I drilled a blindly ending channel about 2 mm. in diameter and 6 mm. long in the substantia compacta of a dog's femur, so that the cavity thus formed did not communicate either with the periosteal or with the endosteal surface of the bone. This cylindrical cavity was filled with India ink, and the open end of it was closed with cement. When the bone was sectioned from four to five weeks after the operation, the foreign material introduced was found intact in the cavity, and no traces of it could be found in the surrounding haversian canals, bone marrow or periosteum. These experiments do not seem to be sufficient to deny the existence of perivascular lymph vessels in the substantia compacta, but I believe that these results strengthen still more my belief that the foreign material introduced into the medullary cavity did not pass to the lymph nodes through the periosteal lymph vessels, but through the channel previously described.

The fact that the lymph in the bone marrow has a tendency to flow in a certain definite direction toward the exit of its lymphatic trunk from the medullary cavity was concluded from an interesting occurrence which we observed during the microscopic examination of bone marrow in which foreign material had been previously introduced. If we drilled a hole through the substantia compacta of a femur at about its middle (between both nutrient foramina) and introduced a few drops of India ink into the medullary cavity, we noticed later the following picture: While India ink could be found in endothelial cells high up around the neck of the femur, very little traces, if any, could be detected in a section through a distal region of the femur, at a distance much closer to the drilled hole than the femoral neck.

The channel described above as the lymphatic trunk draining the bone marrow of the femur is not an exceptional feature in the dog. In an Indian elephant that we had an opportunity to study in the spring of 1924, the foramen through which this vessel passed from the femur was easily found. In that animal, weighing about 6,000 pounds (2720 kg.) this channel was as wide as the lead of a pencil.

The question of the relation of the bone marrow to the lymphatic system is of great importance, not merely from the theoretical, anatomic standpoint; the surgical physiology and pathology of the lymphatic

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system prove this. It is therefore surprising that neither the clinical surgeons nor the pathologic anatomists have ever mentioned in the literature an involvement of the regional lymph nodes described above in inflammatory conditions of the bone marrow, before a periosteal and soft tissue reaction takes place. To quote just one recent statement of a surgeon [12] (Magnus): "When in acute osteomyelitis a phelgmon of the medullary cavity of a long bone develops, as a rule, an inflammatory involvement of the regional lymph nodes does not occur. A bubo, developing following an acute phlegmon of the bone marrow is rather a very rare occurrence, and it is questionable if it ever occurs." [13]

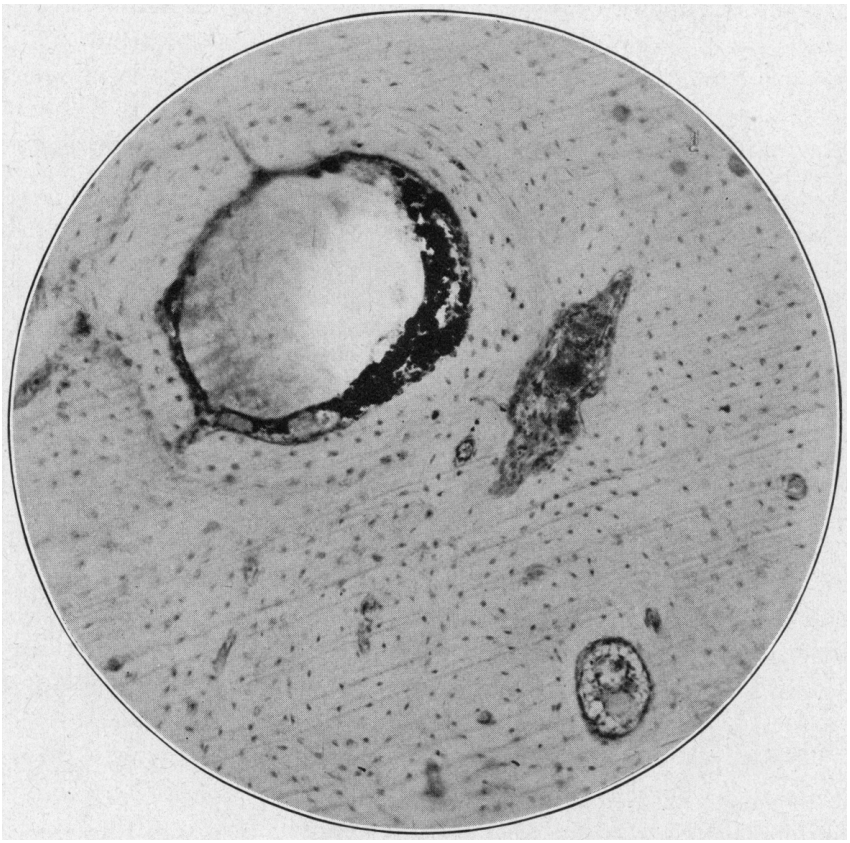

Fig. 4.—The "lymph channel" of the femur passing the substantia compacta; magnification, 100 diameters.

12. Magnus, G.: Die Darstellung der Lymphwurzeln in menschlichen und tierischen Geweben, ihr Verhalten in serösen Häuten und ihre Bedeutung für deren Pathologie, Deutsch. Ztschr. f. Chir. **175**:147, 1922.

13. "Wenn in Verlauf einer akuten Osteomyelitis eine Markphlegmone im Innern eines langen Röhrenknochens sich abspielt werden wir keinesfalls eine entzündliche Schwellung der regionaren Lymphdrüsen als Regel erwarten, im Gegenteil ein Bubo, der sich im Anschluss an eine akute Markphlegmone entwickelt dürfte etwas sehr Ungewöhnliches sein, und es wäre zu untersuchen ob es überhaupt vorkommt."

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This statement well demonstrates the haziness in the minds of different authors on the question of the relationship between bone marrow and the lymphatic system. Arguments emphasizing the fact that bone marrow is lacking in lymph vessels are supported by clinical evidence, which is based on an *a priori* wrong principle. These authorities accept the axillary lymph nodes as regional for the long bones of the upper extremity, and the inguinal lymph nodes as regional for the long bones of the lower extremity. In two cases of acute osteomyelitis, which I had the opportunity to examine at necropsy, the regional lymph nodes as shown by our experiments above were extensively involved.

The definite, direct relationship of the bone marrow to the lymphatic system proved by our experiments is of great importance in the pathology of metastatic epithelial bone tumors. When Von Recklinghausen [14]

TABLE 1.—*Bone Metastases from Malignant Tumors*

Carcinoma of	Occurrence of Metastases, Per Cent.
Skin	0.2
Stomach	2.6
Esophagus	2.7
Uterus	2.9
Breast	16.5
Kidney	25.0
Thyroid	36.9
Suprarenal	50.0
Prostate	70.0

first described in his epoch making monograph the pathologic entity known as skeletal carcinosis, he suggested his circulatory-mechanical theory of the metastatizing of tumors to the skeleton. According to this theory, the vulnerability of the skeletal system is to be ascribed to the ease with which cancer cells, brought by the blood stream, can be retained in the capillaries of the bone marrow. The wide caliber of the capillaries of the bone marrow, the thinness of their walls, their enclosure in a bone shell—all these peculiarities, lead to a retarding of the blood stream in the capillaries and small veins and to an occurrence of peripheral stagnation (ruhende Wandschichten) where the malignant cells can grow and multiply. Neusser [15] has attempted to explain the frequent occurrence of bone metastases in connection with certain varieties of carcinoma by a "blood affinity" (Blutverwandtschaft) between the bone marrow and the prostate, the breast and the thyroid.

14. Von Recklinghausen: Die fibröse oder deformative Ostitis, die Osteomalacie und die osteoplastische Karzinose in ihrer gegenseitigen Beziehungen, Festschrift d. Assistenten f. R. Virchow, 1891.

15. Neusser, E.: Klinisch-hämatologische Mitteilungen, Wien. klin. Wchnschr., 1892, p. 41, 5, No. 3.

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This explanation was later accepted by Paltauf, Bamberger and others. The conception rather vaguely expressed by Neusser is not only merely hypothetical but absolutely not in accord with clinical facts; this will be seen from a few figures on the frequency of bone metastases from malignant tumors in different organs, based on necropsy material.

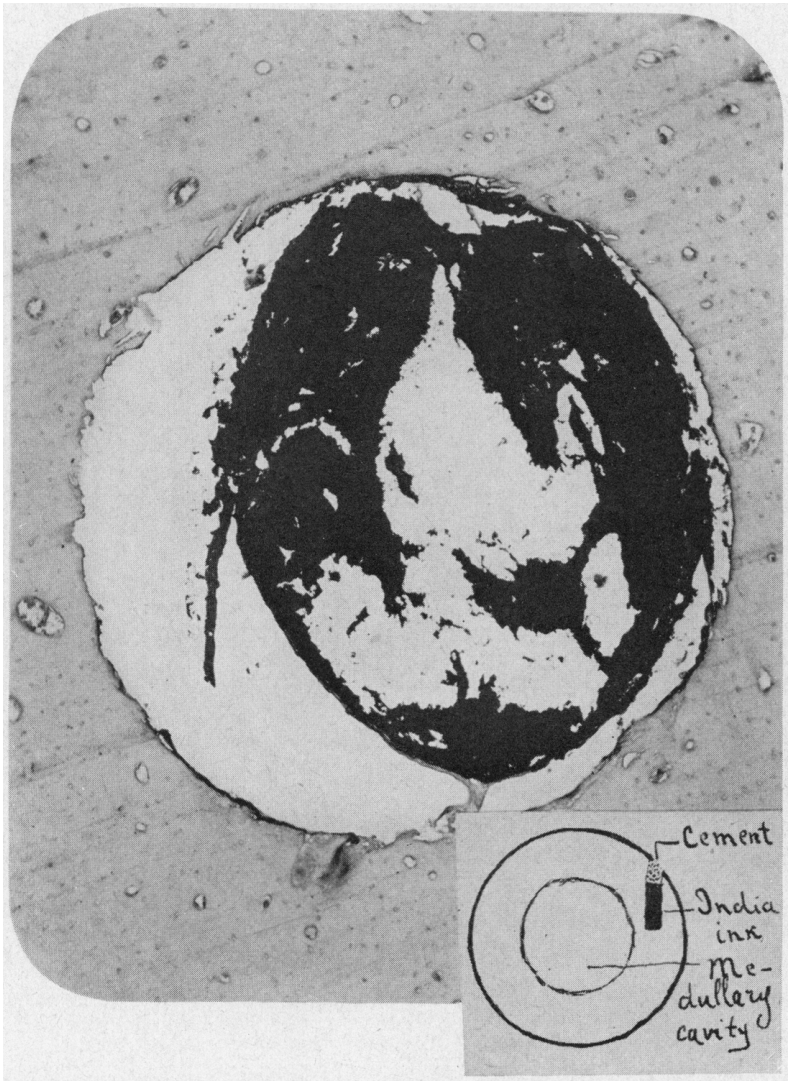

Fig. 5.—A section made through a cavity 2 mm. in diameter and 6 mm. long drilled in the substantia compacta of a dog's femur (magnification, 60 diameters); India ink was introduced, and the opening sealed with cement (insert). The dog was killed two weeks after operation. No absorption of India ink through the substantia compacta can be detected.

According to Schmorl, 7 per cent. would have to be added to all the figures in Table 1, if microscopic examinations of the bones were made. If the occurrence of bone metastases in tumors of the breast, thyroid,

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and prostate has to be explained by a "Blutverwandtschaft" between the bone marrow and these organs, the existence of such a "Blutverwandtschaft" will have to be admitted between the bone marrow and many other organs of the body.

The thirty-five years that have elapsed since the theory of Von Recklinghausen was first suggested have not produced any other facts to support it. The two arguments of the supporters of this conception are still the same: first, the fact that in metastatic carcinoma of bone veins filled with carcinomatous cells are easily found; and second, the general opinion that bone marrow is lacking in lymph vessels. It

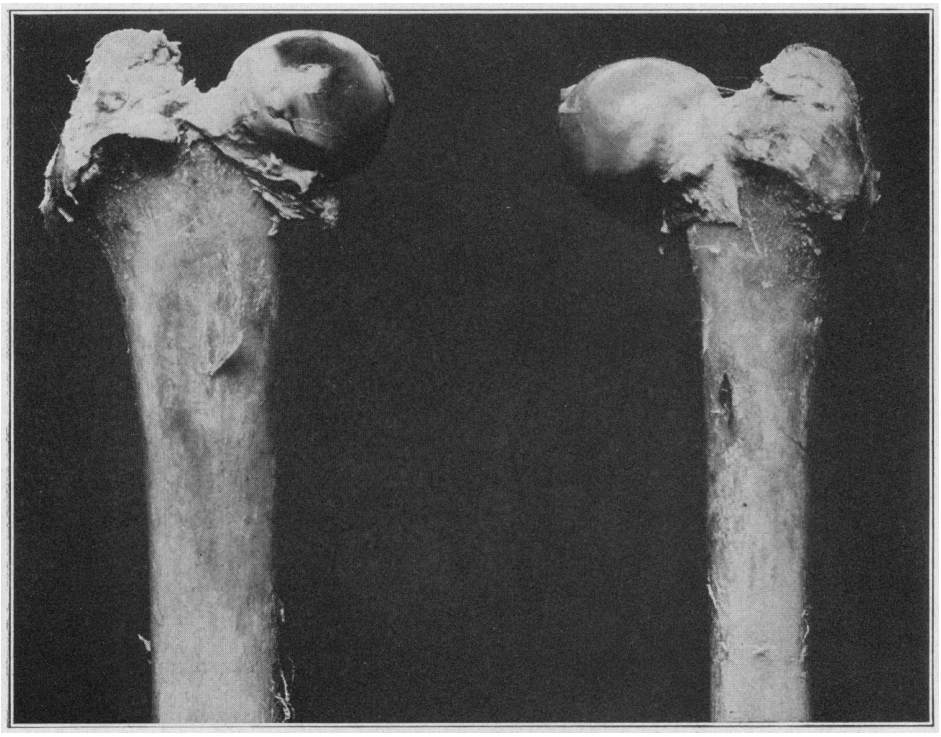

Fig. 6.—Femurs of dogs, showing the "lymph channel"; in the femur to the right, the lymph channel is impregnated with carmin introduced into the medullary cavity three weeks previously.

is well known that carcinomatous cells can be readily found in blood vessels in any protracted case of carcinoma and not merely in skeletal carcinoma. The general belief that the bone marrow has no relation to the lymphatic system was the most forceful argument presented by authorities, who accepted the circulatory-mechanical theory of Von Recklinghausen. W. S. Handley [16] was the only authority who continued to affirm that carcinomatous metastases in the skeleton were in

16. Handley, W. S.: Cancer of the Breast and Its Operative Treatment, London, T. Murray, 1906.

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no way different from similar metastases in other organs, and that the route that these metastases take is the usual one in carcinomatous invasion of the lymphatic system. In view of the general belief of a lack of lymphatics in the bone marrow, Handley expressed the opinion that the carcinomatous cells invade the bones by way of the lymph vessels entering the bone at points of muscle insertions. However, since I have proved that there is a direct relation between the bone marrow and the lymphatic system, there is no need to mention hypothetical lymph vessels entering the bone at points of tendon insertions.

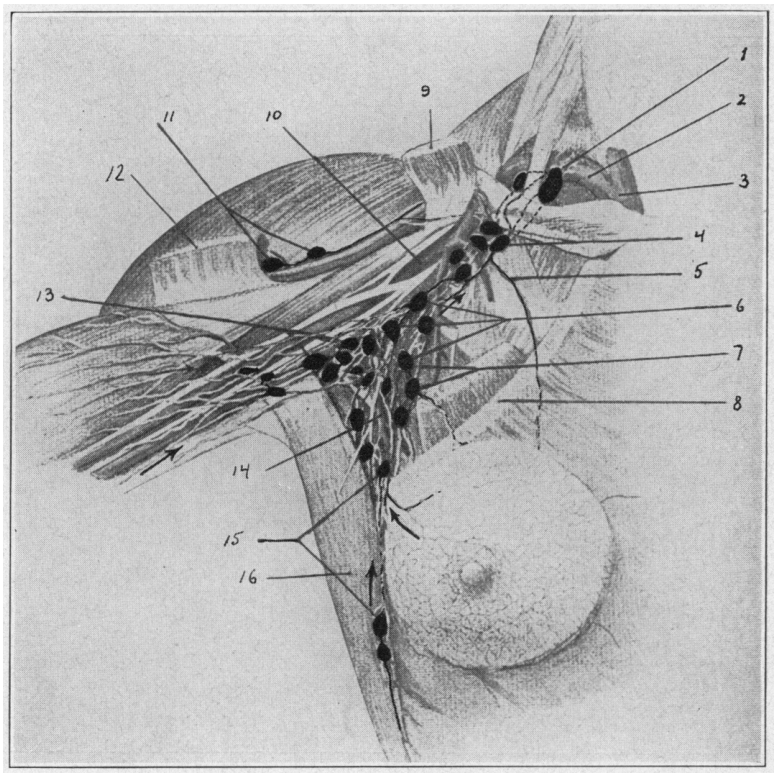

Fig. 7.—Scheme of the axillary and adjoining regional lymph nodes (after a figure from Poirier and Charpy in Anatomie humaine **2**:4) : 1, supraclavicular lymph nodes; 2, subclavian artery; 3, innominate artery; 4, subclavian lymph nodes; 5, mammary lymphatic ending in the subclavian glands (inconstant); 6, central group of the axillary lymph nodes; 7, superointernal portion of the thoracic chain; 8, pectoralis major muscle; 9, pectoralis minor muscle; 10, artery; 11, deltopectoral lymph nodes; 12, pectoralis major muscle; 13, humeral chain of the axillary lymph nodes; 14, thoracodorsalis artery and nerve; 15, inferno-external portion of the thoracic chain; 16, latissimus dorsi muscle.

It is our belief that the direct relationship between the bone marrow and the lymphatic system, proved by our experiments, provides the missing link in the anatomic basis for the lymphogenous theory of the invasion of bone by carcinomatous cells. Carcinoma of the prostate

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leads to an involvement of the regional lymph nodes of the prostate, the middle chain of the external iliac group, the hypogastric group, the lateral sacral group and the promontory group. The hypogastric lymph nodes are, as it has been pointed out above, the regional lymph nodes of the bones of the lower extremity, and invasion of these lymph nodes by carcinomatous cells can easily lead to a similar invasion of these bones by means of a retrograde lymph flow. A similar occurrence may take place from a carcinoma of the breast in relation to the bones of the upper extremity. Figures 7 and 8 illustrate the relationship of the main groups of regional lymph nodes about the bases of the upper and lower extremities.

In our explanation of the possible anatomic path of invasion of the skeleton by carcinomatous cells, I admit as a proved fact the possibility, under certain conditions, of a retrograde centrifugal lymph flow. Since this question of the occurrence of a retrograde lymph flow is still a disputable one, I have carried on experiments to cover it. The prostate in dogs was exposed, and India ink was injected into them. Then, the efferent vessels of the regional lymph nodes of the prostate were ligated. Occasionally, in a few hours, but usually a day or two after the injection, I found the lymphatic accompanying the sciatic nerve in the middle of the thigh injected with India ink. From a study of such lymph nodes, it is known that in carcinomatous involvement, the histologic changes in the lymph nodes frequently lead to occlusions of the efferent vessels similar to those produced in our experiments by ligation. In the early stages of lymph node involvement, carcinomatous cells are found lying in the subcapsular lymph sinuses at the point of entry of the efferent lymphatics, along which the malignant cells have been swept by the lymph stream. Later, these carcinomatous cells compress the pulp and lead to an atrophy of the lymphoid tissue and to an occlusion (obliteration) of the lymph node. At that stage, the carcinomatous cells invade the capsule and the peripheral lymph vessels. This obliteration of the lymph sinuses of the lymph node, equivalent to the ligation of the efferent vessel in our experiments, causes the retrograde lymph flow. Such changes in lymph nodes are not produced by carcinomatous invasion only; a previous inflammatory involvement of a lymph node, or an impregnation of a lymph node with foreign material, such as is seen in bronchial lymph nodes, can lead to the same practical results, obliteration of the lymph spaces of the lymph node—a result that seems to nullify the importance of the respective lymph node as a guard against infection in further life. In such cases, aberrant lymph capillaries develop; these are channels for communication between the efferent and afferent vessels of the obliterated lymph node. These points have been proved experimentally. India ink was injected in the prostate of a dog twice, with an interval of three days between injections. Four weeks

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after the last injection of India ink, carmin was injected in about the same area. Two days after this injection the dog was killed. The regional lymph nodes of the prostate were coal black. No carmin could be detected in them, while the next proximal chain of lymph nodes, the common iliac lymph nodes, contained abundant particles of carmin. India ink, brought to the regional lymph nodes of the prostate in abundant quantities, led to an obliteration of these lymph nodes. The carmin could be forwarded later to the common iliac lymph nodes only by way of lymph capillaries, developed about the obliterated lymph node during the four weeks between the India ink injection and the carmin injection. Such an aberration of the lymph stream readily explains the so-called paradoxical metastasis occurring when cancer skips the regional lymph nodes and yields distant metastases.

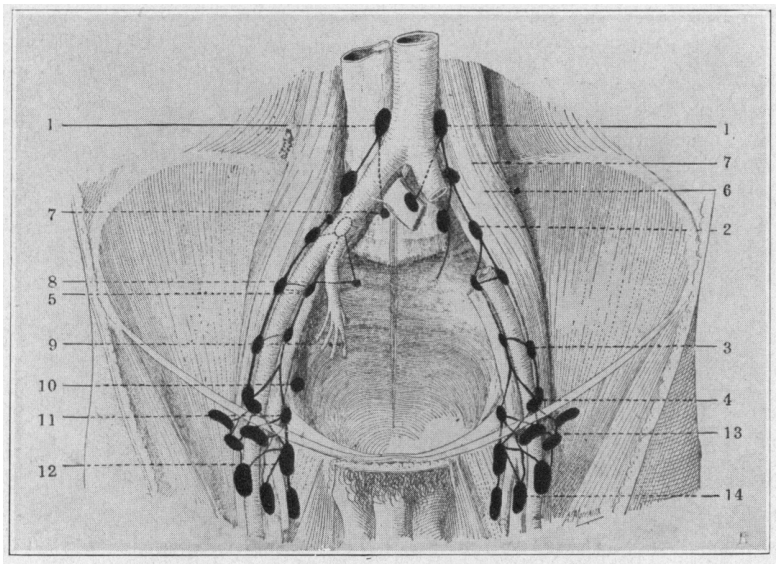

Fig. 8.—Scheme of the iliopelvic lymph nodes (Cunéo and Marcille): 1, inferior glands of the right and left lateral aortic group; 2, common iliac group (external group); 3, middle band of external chain of external iliac glands; 4, retrocrural external glands; 5, gland of the middle chain of external iliac lymph nodes; 6, gland in fossa for the lumbosacral nerve; 7, group of the promontory; 8, lateral sacral group; 9, hypogastric group; 10, gland of the internal chain of external iliac glands; 11, retrocrural internal gland; 12, deep inguinal gland; 13 and 14, superficial inguinal lymph nodes.

Another moot point was before us in the study of the way in which the carcinomatous cells are brought to the bones. A metastatic involvement of the bones on the opposite side from the seat of the primary tumor is frequently found. This could be explained in two ways: First, it is a case of general carcinomatosis, when the circulatory system is overflown with carcinomatous cells; and second, there is a tumor in a more or less early stage, but the carcinomatous cells are brought to the

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opposite side of the body by way of lymph vessels crossing the midline. There has been a tendency among authorities on lymphatics to think that a group of regional lymph nodes drain only the corresponding regional area. Clinical facts have shown that the division in regional areas is merely conditional, and that there can be no doubt that adjoining regional areas, under certain conditions, drain their lymph in the regional lymph nodes of the opposite side. Moreover, it has been noticed by clinicians that an involvement of a group of regional lymph nodes, the axillary lymph nodes of one side, accompanies a carcinoma of the breast of the opposite side. I carried on a series of experiments to investigate the conditions under which such a clinical puzzle can take place.

By an incision (Fig. 9) made in dogs, all the tissues and fasciae covering the ribs and the intercostal muscles were divided. The wound was packed and not closed. At the time of operation carmin was injected in areas indicated on the drawing by the dotted line. The animal was killed two weeks after the operation. The axillary lymph nodes of the left side were inflamed (a reaction to the wound), but no carmin could be found in them. The axillary lymph nodes of the right side were slightly inflamed and contained an enormous amount of carmin particles. The inguinal lymph nodes of the left side as well as those on the right showed an extensive impregnation with carmin, the inguinal lymph nodes of the left side being markedly more impregnated than those of the right side.

Figure 10 illustrates another typical experiment of this series. The incision passed through the whole abdominal wall and all the tissues covering the ribs. The wound was closed, and carmin was injected in the area marked by the dotted line. The animal was killed ten days after the operation. The right axillary lymph nodes contained a large amount of carmin particles. The right inguinal lymph nodes showed a definite impregnation with the stain, but to a less extent than the right axillary. The left inguinal and the left axillary showed an inflammatory reaction (from the wound) but no carmin could be detected in them.

The results of these experiments show that when the normal flow of lymph to the regional lymph nodes of a certain area is radically interfered with (the lymph vessels are cut as in our experiments) or the regional lymph nodes are occluded because of a previous involvement, a reflux lymph stream drives the suspended material (carmin particles in our experiments, carcinomatous cells in metastases) into adjoining areas. Whether these elements are carried through entirely new-formed lymph capillaries or are forced through plexuses of fine lymph capillaries is another question which cannot be answered at present. This question is practically unimportant as far as our study of the production of carcinomatous skeletal metastases is concerned.

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The occurrence of an aberrant and a retrograde lymph stream under the conditions shown in our experiments seems to explain the conspicious relation existing between carcinoma of the thyroid and breast and metastases to the bones of the cranium and the upper extremities, and between carcinoma of the prostate and uterus and the bones of the pelvis and lower extremities. It is known that osteoplastic carcinoma accompanying cancer of the prostate affects most commonly the pelvis and the femur (38.6 per cent. of all cases of skeletal invasion), while that associated with carcinoma of the thyroid and breast usually attacks

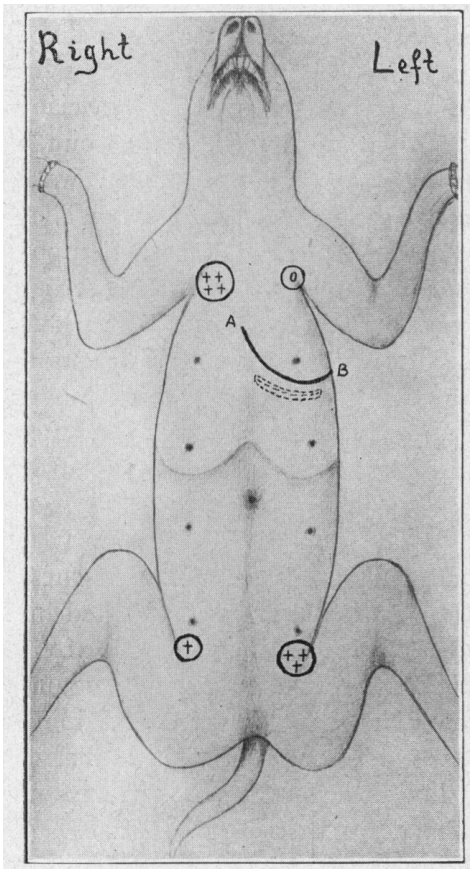

Fig. 9

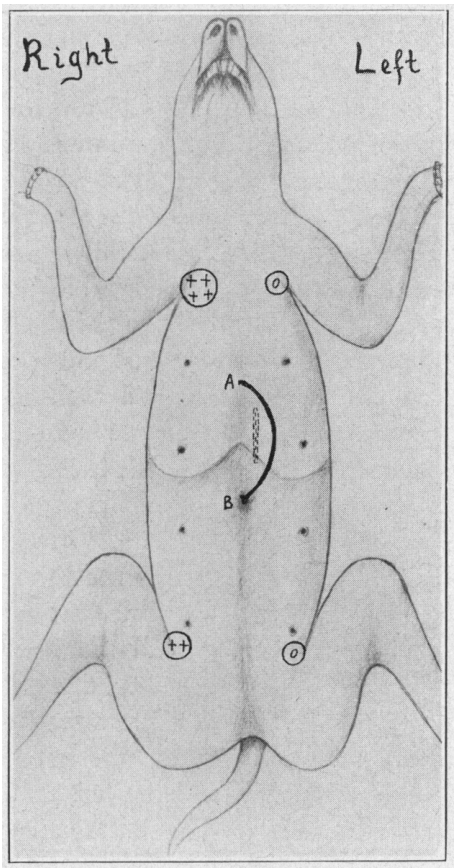

Fig. 10

Fig. 9.—Operation procedure: the incision *A-B* divided all the tissues covering the ribs and the intercostal muscles; the wound was packed, and carmin injected in the area marked by the dotted lines. Two weeks after the operation, the axillary and inguinal lymph nodes contained carmin in the proportion marked on the drawing.

Fig. 10.—Operative procedure: the incision *A-B* passed through the whole abdominal wall and all tissues covering the ribs and intercostal muscles; carmin was injected in the area marked by the dotted lines. Ten days after the operation, the regional lymph nodes (axillary and inguinal) contained carmin in the proportion shown on the drawing.

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the cranium, the sternum, the vertebrae and the bones of the upper extremities (74 per cent. and 68 per cent. of all cases of metastatic invasion of the skeleton). This relationship is understood when the anatomic relation existing between groups of regional lymph nodes (Figs. 7 and 8) is considered.

The not infrequent occurrence of skeletal metastases in the bones of the pelvis and lower extremities in carcinoma of the breast and thyroid, and in the bones of the cranium and upper extremities in carcinoma of the uterus and prostate can be readily explained anatomically as a result of the combination of an aberration of the lymph stream and a reflux lymph stream.

Such, we believe, is the important rôle of the direct relation of the bone marrow to the lymphatic system as an anatomic basis for the lymphogenous theory of skeletal carcinosis. It is hardly necessary to mention that we do not doubt that in protracted cases of carcinoma, in general carcinomatosis, both circulatory systems, the lymph and blood systems, can be and are freely used as means of transportation by the malignant cells swamping the body. The deviations from the normal in the direction and ways of the lymph circulation pointed out above and their rôle in further endlessly complicating the ways of spread of carcinomatous cells remind us of the words frequently spoken by the master surgeon Thiersch in his clinics: "As long as we believe that we can overcome carcinoma with the knife, we shall be defeated." [17]

CONCLUSIONS

The bone marrow is directly related to the lymphatic system. It drains its lymph into certain groups of lymph nodes, the regional lymph nodes of the respective bone.

The regional lymph nodes of the bones of the upper extremity are the cervical lymph nodes in dogs, corresponding to the supraclavicular lymph nodes in man.

The regional lymph nodes of the bones of the lower extremity are the iliac lymph nodes in dogs, corresponding to the external chain of the external iliac group and the hypogastric lymph nodes in man.

The direct relationship existing between the bone marrow and the lymphatic system forms the anatomic basis for the lymphogenous theory of metastatizing of carcinomatous tumors to the bones.

Deviations from the normal in the flow of lymph, namely, the aberration of the lymph stream, the retrograde lymph stream and the reflux lymph flow, can lead to the metastatic spreading through the skeleton of carcinomatous cells transported in the lymph circulation from the primary tumor.

17. "So lange wir glauben das karzinom mit dem Messer bekämpfen zu können werden wir unterliegen."

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